The Ancient Rat

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• Geriatric • Rat • Disease • Husbandry

The past decade has seen an increase in the number of rodents being kept as pets and subsequently in the number of rodent owners seeking veterinary services. The American Veterinary Medical Association (AVMA) reported more than 3 million pet rodents in their 2007 US Pet Ownership & Demographics Sourcebook, nearly double the number reported in the 2001 statistics.[1,2] These new miniature ''companion animals'' have the advantage of being inexpensive to maintain and easily and humanely housed with a minimum of space. The common rat (*Rattus norvegicus*) has become increasingly popular, particularly as novel varieties/genetic mutations have been introduced to the pet market. The average laboratory or domestic pet rat has a life expectancy of approximately 2.5 to 3 years, although 4 years and longer have been reported.[3] Rats are intelligent, trainable, and are responsive to, and even seek out attention from, their caregivers. This behavior emulates that of more traditional companion animals and supports the formation of the human animal bond. Rat owners will seek out quality veterinary medical care to improve and extend the life of their pet. As with traditional companion animals, such as the dog and cat, the aged rat is susceptible to various geriatric diseases, many of which are analogous to geriatric canine and feline maladies. The type and frequency of disease may vary with the strain, stock, or variety of rat.[3]

This article describes disease processes, diagnostics, therapeutics, and husbandry management in the aging rat. The diseases described are not intended to be all inclusive but to represent some of the more common findings. Most of the information on diseases, disease pathology, procedures, and pharmaceutical recommendations and dosages are derived from laboratory animal medicine. Many of the procedural and pharmaceutical recommendations are based on empirical dose ranges extrapolated from other species, trial and error in the laboratory setting, and anecdotal reports. Rat/rodent pet owners should be advised of this and be made aware of potential risks involved in treatment of their pets, particularly in a compromised geriatric animal. References for rodent therapeutics may be found in *The Veterinary Clinics of North*

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America, Exotic Animal Practice,[36] the *ACLAM Formulary for Laboratory Animals*, 3rd edition,[9] and the *Exotic Animal Formulary*, 3rd edition.[10]

Basic physiology and anatomy, symptoms of disease, and methods for physical examination of the rat have been covered by others.[3–5] In the geriatric rat, particular attention should be paid to gait, stiffness and coordination, "lumps and bumps," respiratory effort, evidence of ascites, and fecal or urinary soiling. Porphyrin pigment, a red discoloration, may be seen around the eyes and nares in a stressed or compromised rat of any age. **Table 1** includes a synopsis of normal rat physiologic data.

RENAL DISEASE

Chronic progressive nephrosis/nephropathy (PGN, CPN) is one of the more common causes of death in aged rats and the incidence has been reported as high as 75% in some strains (Sprague Dawley).[6] The disease occurs more frequently in males and is generally of greater severity than the disease in females. Gross lesions of CPN may be found as early as 6 months of age in some strains of rats but housing and diet may play a significant role in incidence. Early gross lesions of the disease demonstrate classic cortical surface pitting. As the disease progresses, interstitial fibrosis, segmental glomerulosclerosis, dilation of cortical and medullary tubules with eosinophilic proteinaceous casts and secondary hyperparathyroidism with dystrophic mineralization in the kidney, gastrointestinal tract, lungs, and large arteries may be found. Hypertension, ascites, and polyarteritis nodosa have been associated with late-stage disease.[3,6] Rats may have severe disease, seem to compensate well, then suddenly decompensate and die. Weight loss, lethargy, and proteinuria (>20 mg/dL) may be the only overt symptoms.[7,8] The astute owner may note polydypsia or polyuria. (Normal urine production in a healthy rat in a 24-hour period is approximately 5.5 mL/100 g body weight; water consumption per 24-hour period is 8–12 mL/100 g body weight)[3,9] Blood chemistry evaluation may reveal increased blood urea nitrogen and creatinine levels, decreased serum albumin/globulin ratio, and hypercholesterolemia. Glomerular filtration rate (GFR) may be decreased by 25% in very aged rats (30 months or greater).[8,9] Differential diagnoses should include chronic bacterial pyelonephritis, congenital hydronephrosis, ischemic injury, and toxic nephrosis.[6]

Diagnostics

Rats and mice typically urinate when handled. Free catch urine samples may be obtained in this way during examination. Alternatively, the bladder is generally easily palpated in the nonobese rat and a bladder tap may be performed using a 25-gauge 0.5-inch needle. Preferably, the fur on the abdomen should be shaved (a battery-operated

Table 1
Data compiled from Laboratory animal medicine, 2nd edition[3] and the Exotic animal formulary, 3rd edition[9]

Heart rate	300–500 beats/min
Blood volume	6.0–6.4 mL/100 g body weight
Respiratory rate	85 respirations/min
Body temperature	37.5°C
Food consumption/24 h	5–6 g/100 g body weight
Water consumption/24 h	8–12 ml/100 g body weight
Basal metabolism rate (400 g rat)	35 kcal/24 h

moustache clipper with a 1-inch blade works well and creates minimal noise) and the skin disinfected before needle tap. An assistant can gently restrain the rat on its back using one hand to restrain the head and forelimbs and the other to extend the rear limbs. The rat's head should be pointed slightly downward to displace the intestines cranially. The bladder may then be digitally isolated with a thumb and forefinger for sampling. Fractious animals should be sedated. The ventral prostate is large and bilobed in the male rat. It lies over the base and neck of the bladder and may completely cover a small bladder. Care should be taken not to hit the prostate and a bladder tap should not be attempted if the bladder is not easily isolated. **Table 2** details reference ranges for normal rat urine.

Blood work may also be performed, although traditional experimental sites for blood collection in the rat, such as orbital bleeds or laceration of tail vessels, may not be aesthetically pleasing in the clinical situation. The lateral caudal tail vein can be easily accessed for obtaining blood samples and administration of fluids and therapeutics. Commercial laboratory rat restrainers, guillotine cones, or towels wrapped around the rat may be used to assist manual restraint during collection. Care should be taken not to restrict the thorax or obstruct the nares and mouth. Isoflurane anesthesia via chamber/facemask may be necessary or advantageous: chamber sedation (3%–4% isoflurane in 100% oxygen) followed by 1.5% to 2% isoflurane in 100% oxygen via facemask. Facemasks may be fashioned from syringe cases. A latex glove finger or dental damn material may be used as a diaphragm over the end. Small cable ties may be used to secure the diaphragm to the cone. Sevoflurane may be preferred to isoflurane, and has worked well in compromised rats because of its rapid induction and emergence from anesthesia. (Sharmon Hoppes, DVM, Texas A&M, College Station, Texas, August 2009, personal communication.) Additional information on anesthesia of rodents may be found in *The Veterinary Clinics of North America, Exotic Animal Practice*,[40] *Anesthesia and Analgesia in Laboratory Animals*,[38] and *Laboratory Animal Anesthesia*.[39] The tail vein may be accessed using a 1-inch 21- or 23-gauge catheter or needle and the blood sample may be obtained by insertion of a capillary tube into the hub of the needle or catheter. Alternatively a few drops of blood may be dripped into a microtainer. The dorsal tarsal vein may also be accessed in the rat. A 27-gauge needle is recommended; 500–1000 μL can be safely taken from the average adult (250 g or more) rat and divided between ethylenediaminetetraacetic acid (EDTA) and serum microtainer tubes. Generally, a single maximum blood draw of 5.5 mL/kg of rat is safe, with a 2-week recovery period before repeating.[10]

Prevention

Laboratory rat strains such as the Sprague Dawley and Fischer 344, known to have increased incidence of CPN, have decreased incidence and severity when on 25%

Table 2
Data created from Laboratory animal medicine, 2nd edition[3] and the Exotic animal formulary, 3rd edition[9]

Urine volume/24 h	5.5 mL/100 g body weight
Urine pH	7.3–8.5
Urine specific gravity	1.022–1.070
Protein	<20 mg/dL; <30 mg/dL
Urine osmolarity	1659 mOsm/kg of H_2O
Urine Na^+:K^+ excretion/24 h	1.63 mEq; 0.83 mEq/100 g body weight

to 30% reduction in caloric intake, relative to ad libitum feeding.[11] It is thought that overfeeding results in prolonged increased renal blood flow and GFR.[12] Although some inbred laboratory strains of rats have been fed commercial rodent diets (protein concentration of 22%–25%) ad libitum, without development of significant renal disease, prevention of overfeeding in pet rats may help to delay the onset and decrease the incidence of CPN.[8]

Treatment

As with the aged dog or cat, treatment is palliative. Lowering the protein content in the diet and supplemental fluids for ''stressed'' rats may ameliorate the situation temporarily (0.9% saline or 50:50 saline/lactated Ringer solution; dosed at 50–100 mL/kg/24 h maintenance dose warmed to body temperature[9]). Recommended dosage volume for fluids is 25 mL/kg maximum per subcutaneous administration; 10–25 mL/kg maximum per intraperitoneal administration using a 25- and 23-gauge needle, respectively.[10] Reducing dietary protein levels lower than 20% to 10% to 14% may also be advantageous.[8] Angiotensin-converting enzyme (ACE) inhibitors have been suggested for associated hypertension.[13]

Nephrocalcinosis (deposition of calcium phosphate in the kidneys) is also seen in aged rats. It is more common female rats and incidence varies with the strain/stock. High levels of dietary calcium or phosphorus, low calcium/phosphorus ratios, or low magnesium may contribute to the disease incidence. Mineral deposition is generally observed histologically at the corticomedullary junction.[3] Clinically advanced cases may demonstrate renal dysfunction, including albuminuria.[6]

GENITOURINARY DISEASE

Urinary calculi of the renal pelvis and urinary bladder has been reported and may be associated with hematuria, cystitis, hydronephrosis, and obstruction. Calculi have been composed of ammonium magnesium phosphate, mixed carbonate and oxalate, and mixed carbonate and phosphate with magnesium and calcium.[14] Water restriction may be associated with formation of calculi.[6] Calculi may occasionally be seen at the tip of the penis and be gently milked out. A small 23- to 25-gauge flexible intravenous catheter may be used as a urinary catheter to back flush obstructive calculi into the bladder to relieve obstruction. Extremely gentle manipulation and plenty of lubricant are required, and a few drops of lidocaine may be mixed in the flushing solution. In the male, the penis should be manually extruded, and after the catheter is placed into the tip the penis should be extended distally to allow advancement over the pubic area. Surgical intervention (cystotomy) may be successfully performed. Supplemental subcutaneous fluids, antibiotics, heat source, and analgesia should be provided. Choice of antibiotics, analgesics, and fluids from referenced sources should be made with consideration of the extent of organ compromise involved. Calculi should not be confused with vesical proteinaceous plugs, secretions from the accessory sex glands of the rat that may also be seen at the tip of the penis or refluxed back into the bladder. In aged rats, these secretions may become hardened and cause irritation and obstruction.

Male Genital Track

Preputial gland adenitis is common in rats older than 12 months.[15] Gland ducts may be distended with inspissated secretion and necrotic debris, and abscesses may also occur. Draining abcesses can be flushed with antibiotic/steroid salves or mild antibacterial solutions. Systemic antibiotics may be administered in more severe

cases. Prostatic hyperplasia and prostatic adenocarcinomas have been seen.[8] Surgical debulking of the prostate, which has multiple lobes in the rat, including tissue ventral, dorsal, lateral to the urethra, and tissue ventral to the seminal vesicle, is a difficult surgery requiring intensive postoperative supportive care. Small tumors located solely in the ventral prostate or seminal vesicle have the best chance for resection but owners should be cautioned that they will most likely return. Prostatic tumors may lead to obstruction of urine flow from the bladder. Testicular atrophy, interstitial (Leydig) cell tumors, dystrophic calcification in degenerating tubules, and polyarteritis nodosa of testicular arteries are also seen in the aged male rat.[8]

Female Genital Track

After 9 months of age, litter size decreases, and the pregnancy rate declines after 12 months of age. Fetal wastage may be as high as 65% by 11 months of age.[3] Hydrometra, pyometra, and cystic endometrial hyperplasia have been reported.[16,17] Surgical intervention, (ovariohysterectomy)may be performed if the rat is otherwise stable.[18] Perioperative analgesics, antibiotics, supplemental heat, and fluid therapy are essential.

MYOCARDIAL DISEASE

Cardiomyopathy has been found to be a major cause of death in aged male rats (>1 year), although there may be no obvious signs of cardiac insufficiency. Twenty-five percent or more of rats of some strains may be affected. Moderate-to-marked ventricular hypertrophy and pale streaks may be visible on gross necropsy. Necrosis of myocardial fibers and infiltration of mononuclear cells are seen histopathologically. The papillary muscles and interventricular septum are most commonly affected.[3,6] Dietary restriction (25%–30% of total caloric intake ad libitum) has been shown to reduce the incidence of this disease in rats.[19] Therapy is supportive, although experimentally, ACE and zinc metalloproteinase inhibitors have been used successfully, to prevent left ventricular remodeling and systolic dysfunction by inhibiting matrix metalloproteinase (MMP-2) activation.[20,21]

DERMATOLOGIC

Thinning and loss of hair, yellowing of the hair in albino strains because of sebum accumulation in the skin and scaley discolored tails may be seen.[22] Yellow material accumulating on the tail and adjacent to the ear may darken with time, possibly from oxidation or bacterial action. Male rats also accumulate brown-pigmented ''scales'' on the skin over the dorsum, tail, and perineum. These scales overlay normal color skin and can be removed. It has been suggested that these scales may be oxidized lipid or amino acids. Gonadectomy/castration can be ''curative.''[3] Orchiectomy of rodents has been described elsewhere but of particular note in the rat is that the inguinal canal must be closed after removal of the testes.[18]

ALVEOLAR HISTIOCYTOSIS

Alveolar histiocytosis is a common incidental necropsy finding in the lungs of aged rats and should not be mistaken for viral pneumonia of rats. Grossly it appears as white-to-tan foci approximately 1 mm in diameter, on the pleural surface. Microscopically subpleural accumulation of foamy macrophages may be seen. The cause is unknown.[3]

POLYARTERITIS NODOSA AND ATHEROSCLEROSIS

Polyarteritis nodosa is a chronic progressive disease of aging rats, occurring in medium-size arteries of the mesentery, pancreas, pancreaticoduodenal artery and

testis. It is a spontaneous disease seen more frequently in males of certain strains (Sprague Dawley and spontaneously hypertensive rats) or in rats with late-stage nephropathy.[6] Atherosclerosis of the aorta, carotids, and coronary arteries may develop in older rats, and has been associated with intensive breeding (siring or whelping 5 or 6 litters in a 9- to 12-month period). Atherosclerosis may not be linked with myocardial degeneration in the rat, but significant coronary artery disease has been linked with acute subendocardial infarction in the rat.[23]

LIVER PATHOLOGY

Bile ductular proliferation and extramedullary hematopoiesis have been seen in older rats.[6]

RETINAL DEGENERATION

Although not specifically an aging change, retinal degeneration is seen in albino rats subjected to light intensities of 130 lux or greater, intensities that are generally harmless to rats with pigmented uveal tracts. Because this is a progressive disease, caused by gradual reduction of the photoreceptor cell nuclei in the outer nuclear layer of the central retina, apparent disturbances in sight or subsequent cataract formation from this may be noted in older rats.[6] Owners with albino rats should be aware of light sensitivity in their pets.

DEGENERATIVE OSTEOARTHRITIS

Articular cartilage erosion of the sternum and femur is seen in aged rats. Osteoarthritis of the tibiotarsal joints and medial femoral condyles is also sporadically seen.[5,6] Decubital ulcers of the plantar surfaces of the hind feet may be seen in aged obese rats housed on wire. Severe cases may lead to chronic periostitis and osteitis. Chronic spondylitis is also seen in geriatric rats. Nonsteroidal antiinflammatories such as meloxicam, carprofen, or flunixin meglumine may offer relief from arthritis. Recommended dosages are varied and therapy may require tailoring the dose to the individual case.[9,10,24,25]

CENTRAL NERVOUS SYSTEM DEGENERATIVE CHANGES

Posterior weakness, disturbances in motor function, including tail dragging, or paresis in the aged rat may indicate radicuoloneuropathy, a degenerative disease of the spinal roots accompanied by atrophy of skeletal muscle in the lumbar region and hind limbs.[24] Incidence in older rats (>24 months) may be as high as 75% to 90%. Demyelination and vacuolation are seen in the lumbosacral roots, most notably in the ventral spinal regions.[6,25] Although no nutritional component has been defined, some advocate supplementation with B complex. B vitamins have been shown to attenuate inflammatory and neuropathic pain effectively in experimental animals.[26–28] Oral and parental forms of B vitamins have been used.

Focal Wallerian degeneration of the spinal cord and segmental demyelination of peripheral nerves, particularly the sciatic nerves, has also been noted. Degeneration of neurons in the brain and spinal cord have also been noted in aged rats.[29]

SKELETAL MUSCLE

Muscles of the hind quarters, especially the gastrocnemius and adductor, may become atrophic and flabby in the geriatric rat. Rats affected by muscular

degeneration may have difficulty in using their rear limbs, develop posterior paresis, paralysis, loss of tail control, urinary incontinence, or atony. Weight loss may also be noted. Histologically, individual muscle fibers are decreased in diameter and there is a prominence of sarcolemmal nuclei secondary to hypertrophy and hyperplasia.[8] It has been suggested that the skeletal muscle lesions are caused by neurogenic atrophy secondary to nerve root and spinal cord lesions (radiculoneuropathy), although skeletal muscle lesions are delayed by caloric restriction and radiculoneuropathy is not.[30,31]

Aged rats suffering from arthritis, neuro, or muscular disease need to be monitored closely to ensure that they are able to access food and water sources with ease. Traction mats or additional bedding material on the bottom of the cage may help with ambulation. Soiling of the perineum may indicate an inability to self-clean. Rats should also be monitored to ensure they are able to urinate and defecate. If they are unable to move the tail well, there may be trauma and subsequent infection and necrosis.

INFECTIOUS DISEASE

The primary infectious disease of concern in the aged pet rat is murine respiratory mycoplasmosis (MRM), the major component of chronic respiratory disease. The causative agent is *Mycoplasma pulmonis.*[32] The infection is generally silent in young animals. Clinical signs in aged rats may include dyspnea, snuffling, chattering, rales, nasal discharge, chromodacryorrhea, and head tilt. Rats with severe middle-ear involvement may spin when suspended by the tail. The disease may be transmitted horizontally by aerosol and direct contact, and vertically in utero.[33] Venereal transmission may be possible. Mycoplasmosis should be differentiated from other bacterial pneumonias (such as cilia-associated respiratory bacillus, *Corynebacterium kutscheri,* and streptococcosis) and from viral mycotic and environmental causes. Mycoplasma may be cultured from exudate in the upper respiratory tract and middle ears.[3,6] Enrofloxacin (10 mg/kg by mouth every 12 hours) combined with doxycycline (5 mg/kg by mouth every 12 hours) have proven efficacious in treatment of MRM.[9]

TUMORS

Mammary tumors are common in older female rats. Of these mammary tumors 80% to 90% are benign fibroadenomas; the remainder are carcinomas. Genetic susceptibility is the most significant factor, although diet and environment may also play a role. Unlike in the mouse, retroviruses do not seem to play a role in development of mammary tumors in rats. Prolactin levels in rats with tumors have been reported to be 25 times higher than virgin females. These tumors may become large and infiltrate locally without metastasis. These tumors may be resected if not too large, but may recur in another mammary gland.[3,6]

Interstitial cell tumors have a high predominance in the males of some strains of rats (see earlier discussion). The testes may be removed surgically.

Pituitary adenoma is a common tumor in aged male and female rats. As with other tumors, genetic factors and diet may play a role. Rats may be asymptomatic or display profound depression and incoordination. It has been suggested that prolactin-producing pituitary tumors may be associated with increased incidence of mammary fibroadenomas.[34]

Large granular lymphocytic leukemia is a major cause of death in some strains of geriatric laboratory rats. Leukocyte counts of 400,000/mL^3 have been seen. Enlarged spleen (which may be palpable), icterus, anemia, weight loss, and depression are characteristic clinical signs.[6,35]

GENERAL HUSBANDRY CONSIDERATIONS IN AGED RATS

The aged rat may have difficulty ambulating because of arthritic, neurologic, or muscular disease. The primary enclosure of these animals should allow for easy access to food and water. Toenails may become overgrown in smooth-bottomed cages and may be a particular problem in aged rats with altered stance and gait caused by arthritis or neuromuscular degeneration. Flooring and bedding should allow adequate traction. Increased urination secondary to renal disease may require more absorbent materials to be used and more frequent cleaning schedules. Compromised animals may have difficulty in maintaining body temperature. Additional bedding material and supplemental heat sources may be necessary. Caution should be taken not to overheat the rat. Heat lamps and heating pads pose greater risks than warm air or water blankets.

Medicating rats can be challenging although sweet medications such as pediatric amoxicillin drops are generally well accepted. Water should be medicated with caution. Rats may avoid drinking medicated water and this risks adequate hydration and inadequate dosing. Mixing a sweet juice with the water may increase palatability. Parental medication, oral medications hidden in sweet food or administered by gavage may be preferred. Flavored medicated rat treats are available commercially for the research arena.

If abdominal or lengthy surgery is necessary in the aged rat, inhalant anesthesia such as isoflurane generally yields a more stable plane of anesthesia than injectable rodent cocktails. Anesthesia methods, sedation, and anesthetic dosages are available in several publications.[9,10,36–40]

Diet and longevity studies in laboratory rats have indicated that caloric intake may be the single greatest influence on the incidence and severity of lesions and longevity.[11,12,19,41] High levels of dietary protein (22% or higher) are associated with a high incidence of chronic nephritis and diets comprised of 20% fat rather than 5% to 10% are life shortening. Additionally, protein over- and undernutrition have been shown to modify neoplasm incidence.[8,42]

SUMMARY

Geriatric disease in the pet rat is a sequela to aging, environment, and genetics and is not generally ''curable.'' At best, the clinician may be able to offer improved quality of remaining life for some patients. The informed clinician, however, may be armed with sufficient information to help the owner of a geriatric rat understand the geriatric disease processes and make an informed decision on humane care for their pet, including selection of euthanasia when treatment options are limited, not effective, or not available.

Biomedical research continues to find new therapies aimed at improving the longevity and quality of life for humans and animals. The rat is central to this research. Research in the rat has included regeneration of spinal cord nerves and brain neurons, new pharmaceutical and gene therapy for heart failure, new treatments for chronic renal failure and organ transplantation.[43–45] The laboratory rat is often the first species in which proof of concept, dosing, and efficacy is verified. Pet rat medicine has the opportunity to access cutting-edge therapies for the companion rat, developed first in and for the rat.

REFERENCES

1. AVMA. Market research statistics. U.S. pet ownership & demographics sourcebook. Schaumburg (IL): American Veterinary Medicine Association; 2001.

2. AVMA. Market research statistics. U.S. pet ownership & demographics sourcebook. Schaumburg (IL): American Veterinary Medicine Association; 2007.
3. Kohn DF, Clifford CB. Biology and disease of rats. In: Fox JG, Anderson LC, Loew FM, et al, editors. Laboratory animal medicine. 2nd edition. New York: Academic Press; 2002. p. 121–65.
4. Davaiu J. Clinical evaluation of rodents. Veterinary Clin North Am Exot Anim Pract 1999;2(2):429–45.
5. Bivin WS, Crawford M, Brewer NR. Morphophysiology. In: Baker HJ, Lindsey JR, Weisbroth SH, editors. The laboratory rat, vol. 1. 1st edition. New York: Academic Press; 1979. p. 74–103.
6. Percy DH, Barthold SW. Rat. In: Pathology of laboratory rodents & rabbits. 2nd edition. Ames (IA): Iowa State University Press; 2001. p. 107–58.
7. Gray JE, Weaver RN, Purmalis A. Ultrastructural observations of chronic progressive nephrosis in the Sprague-Dawley rat. Vet Pathol 1974;11:153–64.
8. Anver MR, Cohen BJ. Lesions associated with aging. In: Baker HJ, Lindsey JR, Weisbroth SH, editors. The laboratory rat, vol. 1. 1st edition. New York: Academic Press; 1979. p. 378–99.
9. Rodents. In: Carpenter JW, editor. Exotic animal formulary. 3rd edition. St Louis (MO): Elsevier Inc; 2005. p. 376–408.
10. Hawk CT, Leary SL, Morris TH, in association with the American College of Laboratory Animal Medicine. Formulary for laboratory animals. 3rd edition. Ames (IA): Blackwell Publishing; 2005. p.163, 171.
11. Keenan KP, Soper KA, Hertzog PR, et al. Diet, overfeeding, and moderate dietary restriction in control Sprague-Dawley rats: 2. Effects on age-related proliferative and degenerative lesions. Toxicol Pathol 1995;23:287–302.
12. Gumprecht LA, Long CR, Soper KA, et al. The early effects of dietary restriction on the pathogenesis of chronic renal disease in Sprague-Dawley rats at 12 months. Toxicol Pathol 1993;21:528–37.
13. Leenen FD, Skarda V, Yuan B, et al. Changes in cardiac ANGII post myocardial infarction in rats: effects of nephrectomy and ACE inhibitors. Am J Phsyiol Heart Circ Physiol 1999;276:317–25.
14. Patterson M. Urolithiasis in the Sprague-Dawley rat. Lab Anim 1979;13:17–20.
15. Ekstrom ME, Ewald PE. Chronic purulent preputial gland adenitis in the male laboratory rat. Am Assoc Lab Anim Sci. Joilet, Illinois, 1975. Abstr no 10; Publ 75–2.
16. Franks LM. Normal and pathological anatomy and histology of the genital tract of rats and mice. In: Cotchin E, Roe FJ, editors. Pathology of laboratory rats and mice. Philadelphia: Davis; 1967. p. 469–99.
17. Wolfe JM, Burack E, Lensing W, et al. The effects of advancing age on the connective tissue of the uterus, cervix and vagina of the rat. Am J Anat 1942; 70:135–65.
18. Jenkins JR. Surgical sterilization in small mammals. Veterinary Clin North Am Exot Anim Pract 2000;3(3):617–27.
19. Keenan KP, Soper KA, Smith PF, et al. Diet, overfeeding and moderate dietary restriction in control Sprague-Dawley rats: 1. Effects on spontaneous neoplasms. Toxicol Pathol 1995;23:269–86.
20. Brower GL, Levick SP, Janicki JS. Inhibition of matrix metalloproteinase activity by ACE inhibitors prevents left ventricular remodeling in a rat model of heart failure. Am J Physiol Heart Circ Physiol 2007;292:3057–64.
21. Wohlgemuth SE, Julian D, Akin DE, et al. Autophagy in the heart and liver during normal aging and calorie restriction. Rejuvenation Res 2007;10:281–92.

22. Elwell MR, Stedham MA, Kovatch RM. In: Boorman GA, Eustis MR, Elwell CA, et al, editors. Pathology of the Fischer rat: reference and atlas. San Diego (CA): Academic Press; 1990. p. 261–77.
23. Wexler BC. Spontaneous coronary arteriosclerosis in repeatedly bred male and female rats. Circ Res 1964;14:32–43.
24. Witt CJ, Johnson LK. Diagnostic exercise: rear limb ataxia in a rat. Lab Anim Sci 1990;40:528–9.
25. Krinke GJ. Spontaneous radioneuropathology, aged rats. In: Jones TC, Mohr U, Hunt RD, et al, editors. Monographs on pathology of laboratory animals: nervous system. New York: Springer-Verlag; 1988. p. 203–8.
26. Medina-Santillan R, Reyes-Garcia G, Rocha-Gonzalez HI, et al. B vitamins increase the analgesic effect of ketorolac in the formalin test in the rat. Proc West Pharmacol Soc 2004;47:95–9.
27. Jolivalt CG, Mizisin LM, Nelson A, et al. B vitamins alleviate indices of neuropathic pain in diabetic rats. Eur J Pharmacol 2009;612(1–3):41–7.
28. Song XS, Huang ZJ, Song XJ. Thiamine suppresses thermal hyperalgesia, inhibits hyperexcitability and lessens alterations of sodium currents in injured, dorsal root ganglion neurons in rats. Anesthesiology 2009;110(2):387–400.
29. Van Steenis G, Kroes R. Changes in the nervous system and musculature of old rats. Vet Pathol 1971;8:320–32.
30. Marzettie E, Carter CS, Wohlgemuth SE, et al. Changes in IL-15 expression and death-receptor apoptotic signaling in rat gastrocnemius muscle with aging and life-long calorie restriction. Mech Ageing Dev 2009;130(4):272–80.
31. Pollard M, Kajima J. Lesions in aged germfree Wistar rats. Am J Pathol 1970;61: 25–32.
32. Kohn DF, Kirk BE. Pathogenicity of *Mycoplasma pulmonis* in laboratory rats. Lab Anim Care 1969;19:321–30.
33. Lindsey JR, Baker HJ, Overcash RG, et al. Murine chronic respiratory disease: significance as a research complication and experimental production with *Mycoplasma pulmonis*. Am J Pathol 1971;64:675–716.
34. Sandusky GE, Van Pelt CS, Todd GC, et al. An immunocytochemical study of pituitary adenoma and focal hyperplasia in old Sprague-Dawley and Fischer 344 rats. Toxicol Pathol 1988;16(3):376–80.
35. Rosol TJ, Stromberg PC. Effects of large granular lymphocytic leukemia on bone in F344 rats. Vet Pathol 1990;27:397–403.
36. Adamcak A, Otten B. Rodent therapeutics. Veterinary Clin North Am Exot Anim Pract 2000;3(1):221–38.
37. Yale Animal Resources Center. Comparative medicine. Vet Clin Serv Drugs Dosages 2009;1–4.
38. Wixon SK, Smiler KL. Anesthesia and analgesia in rodents. In: Kohn DF, Wixson SK, White WJ, et al, editors. Anesthesia and analgesia in laboratory animals. 1st edition. New York: Academic Press; 1997. p. 165–204.
39. Flecknell PA. Laboratory animal anesthesia. A practical introduction for research workers and technicians. San Diego (CA): Academic Press; 1996.
40. Cantwell SL. Ferret, rabbit and rodent anesthesia. Veterinary Clin North Am Exot Anim Pract 2001;4(1):169–91.
41. Anver MR, Cohen BJ. Nutrition. In: Baker HJ, Lindsey JR, Weisbroth SH, editors. The laboratory rat, vol. 1. 1st edition. New York: Academic Press; 1979. p. 123–52.
42. Ross MH, Bras G. Influence of protein under- and over-nutrition on spontaneous tumor prevalence in the rat. J Nutr 1973;103:944–63.

43. Gage FH, Dunnett SB, Stenevi U, et al. Aged rats: recovery of motor impairments by intrastriatal nigral grafts. Science 1983;221:966–9.
44. Carter CS, Leeuwenburgh CL, Daniels M, et al. Influence of calorie restriction on measures of age-related cognitive decline: role of increased physical activity. J Gerontol A Biol Sci Med Sci 2009;64(8):850–9.
45. Thomas Jefferson University. Gene therapy reversed heart damage in rats with heart failure. Science Daily. December 31, 2008.